Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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The Reply

We recognize the attempts by Korman and McMahon to appraise and dismiss evidence with respect to individual medical therapies as the human suffering, hospitalizations, and deaths continue to mount in the coronavirus disease 2019 (COVID-19) pandemic. In an emergency response to the COVID worldwide pandemic, we believe it is more prudent to act now based on clinical judgment with the early use of therapies based on the pathophysiology of severe acute respiratory coronavirus 2 (SARS-CoV-2) infection and COVID-19 illness as disclosed. More than 50,000 publications have provided therapies with a well-understood and acceptable safety profile. We fully expect the algorithm and associated evidence to be revised and updated over time.[1] An example of such an update is a recent meta-analysis from Ladapo et al from the available 5 randomized clinical trials enrolling 5577 ambulatory patients treated early in the course of infection with hydroxychloroquine. Hydroxychloroquine was associated with a 24% relative risk reduction in COVID-19 infection, hospitalization, or death ($P = .025$, relative risk 0.76 [95% confidence interval, 0.59-0.97]).[2] Another critical update is a growing body of evidence supporting favipiravir, an oral polymerase inhibitor, as an early treatment for SARS-CoV-2 infection.[3] Favipiravir has been approved for ambulatory administration in Italy, Saudi Arabia, United Arab Emirates, Turkey, Bangladesh, and Egypt and has been previously in use in Japan, Russia, Ukraine, Uzbekistan, Moldova, and Kazakhstan.[4] We await the results of studies testing combinations of hydroxychloroquine, favipiravir, and other agents that have activity against SARS-CoV-2.

Another addition to the future treatment of SARS-CoV-2 may be ramatroban because as pointed by Chiang and Gupta, COVID-19 illness may trigger the production of prostaglandin D_2, resulting in activation of cyclooxygenase 1 and 2 and the generation of thromboxane A2.[5] This promising drug, which is commercially available in Japan for allergic rhinitis, may be a more rational choice than aspirin early in the course of COVID-19 illness because it could be better positioned to handle the interface between inflammation and vascular thrombosis.[6] We look forward to the results of studies testing single and combinations of antiplatelet and antithrombotic agents in higher-risk patients with COVID-19.

In summary, we believe the COVID-19 pandemic warrants an emergency response from doctors to patients in the community. As reports of clinical studies are published in the years to come we welcome revisions to the treatment algorithm concerning viral replication and damage, inflammation and cytokine storm, and vascular thrombosis. Our view at present is that clinical judgment and early ambulatory treatment with multiple agents at the onset of SARS-CoV-2 infection addressing all 3 principles of COVID-19 pathophysiology in a well-designed regimen is a sagacious approach to the newly diagnosed patient with COVID-19. The overarching goal of early ambulatory treatment is to reduce COVID-19 hospitalizations and death. With more than 35 million cases and 1 million fatalities, it is no longer tenable in any country to withhold early ambulatory treatment in favor of late-stage hospitalization, complications, and death.

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References

1. McCullough PA, Kelly RJ, Ruocco G, et al. Pathophysiological Basis and Rationale for Early Outpatient Treatment of SARS-CoV-2 (COVID-19) Infection. *Am J Med* 2021;134:16–22.
2. Ladapo J, McKinnon JE, McCullough PA, Risch H. Randomized controlled trials of early ambulatory hydroxychloroquine in the prevention of COVID-19 infection, hospitalization, and death: meta-analysis [e-pub ahead of print]. *MedRxiv*. Accessed December 24, 2020. doi: https://doi.org/10.1101/2020.09.30.20204693.

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3. McCullough PA. Favipiravir and the need for early ambulatory treatment of SARS-CoV2 Infection (COVID-19). *Antimicrob Agents Chemother* 2020;64:e02017–20. https://doi.org/10.1128/AAC.02017-20.
4. Agrawal U, Raju R, Udwadia ZF. Favipiravir: a new and emerging antiviral option in COVID-19. *Med J Armed Forces India* 2020;76:370–6. https://doi.org/10.1016/j.mjafi.2020.08.004.
5. Gupta A, Chander Chiang K. Prostaglandin D_2 as a mediator of lymphopenia and a therapeutic target in COVID-19 disease. *Med Hypotheses* 2020;143:110122. https://doi.org/10.1016/j.mehy.2020.110122.
6. Singhania N, Bansal S, Nimmatoori DP, Ejaz AA, McCullough PA, Singhania G. Current overview on hypercoagulability in COVID-19. *Am J Cardiovasc Drugs* 2020;20:393–403. https://doi.org/10.1007/s40256-020-00431-z.